REMARKS

Amendment

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Double Patenting

Claims 1, 2, 5, 6, 8, 12 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent 6,210,946. Applicants hereby submit a terminal disclaimer to obviate the double patenting rejection.

The 35 U.S.C. §112 Rejection

Claims 1-6, 8-15 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The present invention discloses a method of creating a recombinant adenoviral vector that lacks endogenous fiber tropism

and possesses a novel tropism by replacing the fiber protein with an external trimerization motif to maintain trimerization of the knobless fiber, and simultaneous introducing into the fiber a ligand capable of targeting the virion to a novel receptor. Applicants reiterate that the present invention has demonstrated successful replacement of the shaft region of the adenoviral fiber protein with another trimeric protein. Specifically, a triple β-spiral held together with intra- and inter-chain hydrogen bonding was replaced with a α-helical segment which is a parallel triple coiled-coil structure stabilized by inter-chain hydrophobic and ionic interactions. The present invention teaches and claims the replacement of the trimeric fiber protein with another trimeric protein. Applicants submit that there is sufficient enablement provided in the specification and one of ordinary skill in the art would be able to make similar replacement without undue experimentation.

The Examiner has not provided any evidence to show unpredictability or difficulties of replacing the fiber shaft with another trimeric protein. The Examiner cited the reference of Wickham et al. However, Wickham et al. did not teach or suggest replacing the fiber shaft of the fiber protein with another trimeric protein as claimed herein. Wickham et al. only taught inserting

peptide motifs into the fiber knob at the C-terminal of the fiber protein (see Wickham et al., Figure 1). The present invention teaches, *inter alia*, replacing the whole trimeric fiber shaft with another trimeric protein, whereas Wickham et al. teaches keeping the original fiber shaft and inserts peptide motif into the fiber knob at the end of the fiber protein. Hence, the modification disclosed in Wickham et al. is different and distinct from the modification disclosed by the Applicants' specification.

The Examiner contends that by merely replacing the fiber protein with one of coiled-coil secondary structure, it will require undue experimentation to test if the replacement protein resulted in novel tropism and one that is able to trimerize. Applicants respectfully disagree. First of all, the present invention does not merely teach replacing the fiber protein with one of coiled-coil secondary structure. The instant specification teaches replacing the fiber shaft with a trimeric protein. By definition, a trimeric protein is able to trimerize. Secondly, novel tropism is not determined by the replacement trimeric protein. Novel tropism is conferred by a targeting ligand which is attached to the end of the replacement trimeric protein. The function of the replacement trimeric protein is simply to hold up the targeting ligand away from the surface of the

adenovirus. Hence, there is no need for undue experimentation to determine if the replacement protein would result in novel tropism.

The Examiner contends that the claims are too broad. Applicants has amended claim 1 to recite a fiber replacement protein comprising a) an amino-terminal portion comprising an adenoviral fiber tail domain that associates with the penton base of the adenovirus; b) a chimeric rod-like, trimeric protein that provides trimerization function, wherein said rod-like trimeric protein has a diameter comparable to the native fiber protein of wild type adenovirus; and c) a carboxy-terminal portion comprising a targeting ligand. Applicants submit that the scope of the instant claim 1 has a reasonable correlation to the scope of the enablement provided. Accordingly, Applicants request that the rejection of claims 1-13 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 14-15 are drawn to an adenoviral vector of the present invention carrying the HSV-TK gene and using this adenoviral vector to kill tumor cells according to the HSV-TK/gangliclovir protocol. The HSV-TK/ganciclovir cytotoxic method is currently included in a number of gene therapy protocols and clinical trials. The Examiner also acknowledges that the HSV-TK/gangliclovir protocol is well known in the art. Therefore, Applicants submit that

no undue experimentation is required to administer the adenoviral vector of the present invention to kill tumor cells according to the HSV-TK/gangliclovir protocol. Using the adenovirus of the present invention in the HSV-TK/ganciclovir method is an improvement over the prior art methods because of the enhanced targeting capability of the claimed adenovirus. Applicants submit that the scope of claim 15 has a reasonable correlation to the scope of the enablement provided. Accordingly, Applicants respectfully request that the rejection of claims 14-15 under 35 U.S.C. §112, first paragraph, be withdrawn.

This is intended to be a complete response to the Final Office Action mailed June 19, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (amended) An adenovirus (Ad) with novel vector tropism and ablation of native Ad receptor tropism due to the expression of a fiber replacement protein, said fiber replacement protein comprises:

a) an amino-terminal portion comprising an adenoviral fiber tail domain that associates with the penton base of the adenovirus;

b) a chimeric rod-like, trimeric protein that provides trimerization function, wherein said rod-like trimeric protein has a diameter comparable to the native fiber protein of wild type adenovirus; and

c) a carboxy-terminal portion comprising a targeting ligand.

Claim 8 has been amended as follows:

8. (amended) The adenovirus of claim 1, wherein said rod-like, trimeric ~~fiber replacement~~ protein is selected from the group consisting of trimeric structural proteins, trimeric viral proteins and trimeric transcription factors.

Claim 10 has been amended as follows:

10. (amended) The adenovirus of claim 1, wherein said rod-like, trimeric ~~fiber replacement~~ protein contains ~~is~~ neck region peptide from human lung surfactant D.